



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>C07D 475/08</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/24789</b> <b>(43) International Publication Date:</b> 11 June 1998 (11.06.98)
<b>(21) International Application Number:</b> PCT/US97/21743 <b>(22) International Filing Date:</b> 2 December 1997 (02.12.97) <b>(30) Priority Data:</b> 60/032,250 2 December 1996 (02.12.96) US <b>(71) Applicant (for all designated States except US):</b> BIONUMERIK PHARMACEUTICALS, INC. [US/US]; Suite 1250, 8122 Datapoint Drive, San Antonio, TX 78229 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> HAUSHEER, Frederick, H. [US/US]; 203 Kendall Parkway, Boerne, TX 78015 (US). REDDY, Dasharatha [IN/US]; 1715 Junction Ridge, San Antonio, TX 78248 (US). <b>(74) Agent:</b> DODD, Thomas, J.; BioNumerik Pharmaceuticals, Inc., Suite 1250, 8122 Datapoint Drive, San Antonio, TX 78229 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PROCESS FOR MAKING $\gamma$ -METHYLENE-10-DEAZAAMINOPTERIN (MDAM) <b>(57) Abstract</b> <p>A process to synthesize the dihydrofolate reductase inhibitor, 4-amino-4-deoxy-10-deazaaminopterin (MDAM). The process synthesizes the key intermediate, pteric acid in 5 steps, and uses commonly available starting materials. The steps include the formation of a 6-substituted pteridine, followed by alkylation, hydrogenation, and hydrolysis steps to form pteric acid from the starting material which is tetraamino pyrimidine, or a salt thereof.</p>		

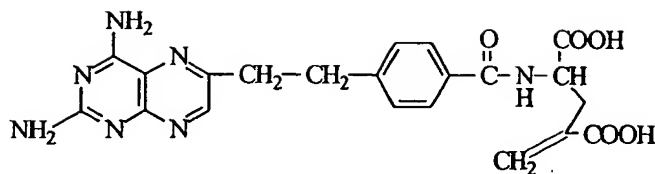
## FIELD OF THE INVENTION

10 BACKGROUND OF THE INVENTION

MDAM is a potent inhibitor of dihydrofolate reductase (DHFR). The therapeutic value of MDAM as an antitumor agent has been well documented in recent literature, as have its increased specificity and reduced toxicity, particularly when compared to analogs, such as methotrexate (MTX). MDAM is currently undergoing Phase I clinical trials at Johns Hopkins University as an antitumor compound.

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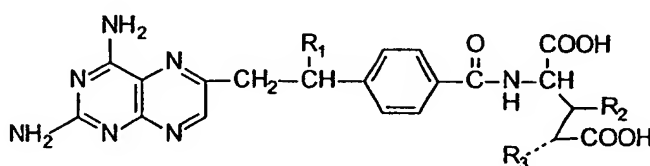
(I)



The general formula for known active derivatives of MDAM is seen below as Formula II:

5

(II)



wherein  $R_1$  is hydrogen or lower alkyl;

$R_2$  is hydrogen or hydroxy;

$R_3$  is hydrogen or methylene; and

10

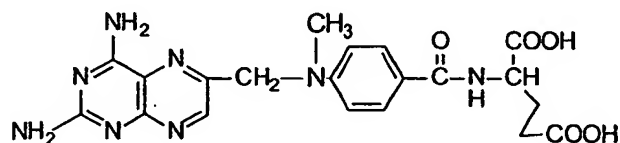
the dashed line indicates a single bond or a double bond.

MDAM is similar in structure to the known antitumor and anti-inflammatory drug methotrexate seen below as

Formula III:

15

(III)



MDAM specifically inhibits dihydrofolate reductase to a far greater extent than MTX. Further, MDAM does not undergo the polyglutamylation common to MTX and derivatives, thereby reducing the toxicity of MDAM far below that of MTX. The greater efficacy and reduced toxicity of MDAM (compared to MTX and derivatives thereof) has been well established for many years now.

B. Current Synthetic Procedures For Making MDAM

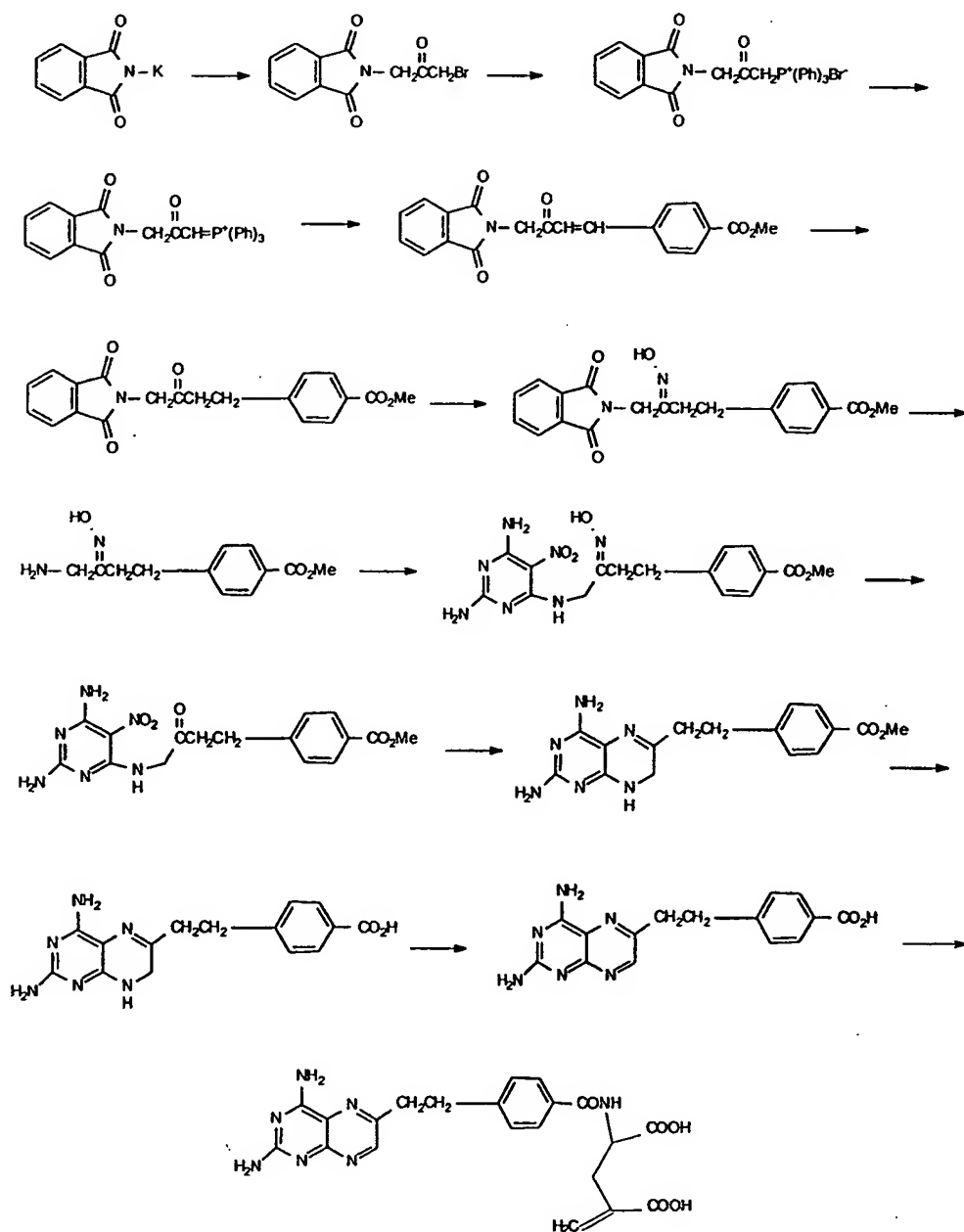
The current process for making MDAM involves a complex 11 step procedure to make the key intermediate, plus an additional three steps to produce the key intermediate diethyly-methylene glutamate), and a final coupling step, followed by the hydrolysis of the ester to MDAM. The prior processes to make the key intermediate, and/or MDAM or derivatives are outlined in the above mentioned U.S. Patents, and in several publications known in the literature, the most notable being Nair, *J. Org. Chem.*, 50:1879, 1985, which publication recites the process shown below as Scheme I.

Further, the previous process for preparing MDAM required the nitration of 2,4-diamino-6-chloro-pyrimidine (a necessary reagent), which was a difficult, time-

consuming, step in the process. A schematic depiction of the prior process is shown below as Scheme 1, and is intended to illustrate the complexity and difficulty previously associated with synthesizing MDAM.

5

Scheme 1



As shown in Scheme 1, the prior art process for synthesizing MDAM requires a number of awkward and time-consuming maneuvers to produce the desired product. The most awkward and time-consuming step is the required  
5 nitration of 2,4-diamino-6-chloro-pyrimidine, which is necessary for the eighth step in the process, the addition of the pyrimidine ring with the 5- and 6-positions having attached nitrogen groups to enable its later conversion to the required pteridine fused ring  
10 group.

The prior art processes to synthesize MDAM were further limited in their adaptability to bulk manufacturing. Cost effectiveness, yield and purity are significant considerations in the bulk manufacture of any  
15 pharmaceutical product, and the prior processes employed to synthesize MDAM were neither cost effective nor did they generate acceptable yields of product.

#### SUMMARY OF THE INVENTION

20

The process described by this invention delivers a highly efficient, convergent process for the synthesis of MDAM and useful derivatives thereof. The inventive

process reduces the number of steps to produce the pterioic acid intermediate from 11 to 5, and further, significantly increases the yield and purity of the end product when compared with prior processes employed to  
5 synthesize these useful compounds.

As stated above, the inventive process involves a five step process to produce the pterioic acid intermediate, which is then coupled to an ester of  $\gamma$ -methylene glutamic acid, and finally hydrolyzed to form  
10 the desired end product in a highly pure form.

The process begins with the conversion of 2,4,5,6-tetraaminopyrimidine to the corresponding pteridine intermediate. After bromination and alkylation of this 6-hydroxymethyl pteridine intermediate to form a 9,10-dehydro pterioic acid ester, reduction of the 9,10-double  
15 bond produces pterioic acid ester, and then hydrolyzing the ester to form pterioic acid (the key intermediate), coupling with  $\gamma$ -methylene glutamic acid ester and hydrolyzing the resulting compound (the diester of MDAM)  
20 yields MDAM in very high yield.

The schemes and specific examples for carrying out the inventive process are illustrated in the detailed description set forth below.

It is an object of this invention to provide for a highly efficient and convergent process for synthesizing MDAM and useful derivatives thereof.

Another object is to provide for a process for  
5 synthesizing MDAM and derivatives, which process is readily adaptable to GMP conditions.

Another object is to provide for a process for synthesizing MDAM which is time efficient, cost effective, and produces MDAM in sufficiently high yield.

10 Other objects will become apparent from a reading of the following detailed description.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 The preferred embodiments herein described are not intended to be exhaustive or to limit the invention to the precise details disclosed. They have been chosen and described to explain the principles of the invention, and the application and practical use thereof, so that those  
20 skilled in the art may understand its teachings.

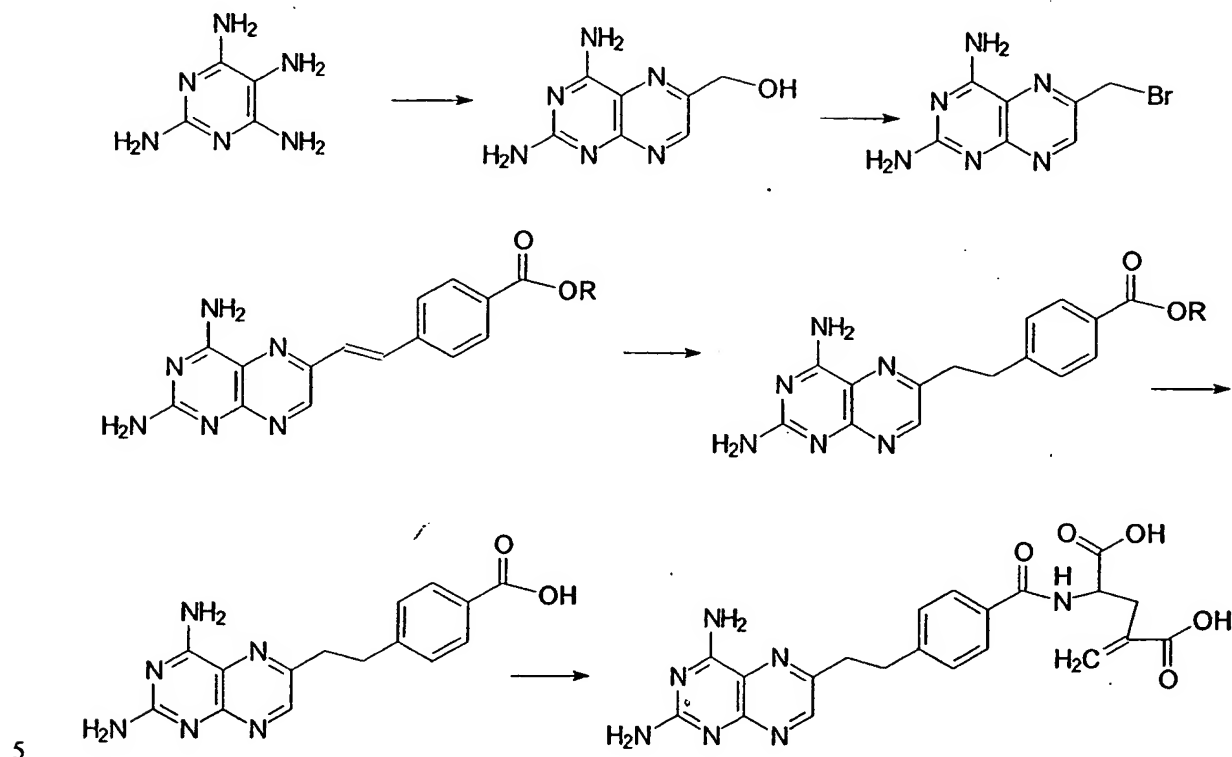
The process of this invention is designed to produce, in substantially pure form, the antitumor agent  $\gamma$ -methylene-10-deazaaminopterin (MDAM). The general



process described by this invention is shown below as

Scheme II:

Scheme II



As shown in Scheme II, the starting material is 2,4,5,6-tetraamino pyrimidine (a). The starting material is preferably obtained as a salt of the actual compound.

10 Most preferred is the sulfate salt, which compound is available commercially from Aldrich Chemical Company and others.

This initial step in the process is carried out according to published conditions in Baugh, et al, *The Journal of Organic Chemistry*, Volume 29: p 3610 (1969).

15

The intermediate 6-hydroxymethyl pteridine (b) is the resultant compound, which is formed by a closure of the fused 'B' ring of the pteridine molecule by condensation of 2,4,5,6-tetraamino pyrimidine and dihydroxy acetone.

- 5 The preferred reagents are those which support these conditions and the ring formation, preferably ketols, and in the most preferred case, 1,3-dihydroxy-2-propanone.

The 6-hydroxymethyl pteridine (b) is then brominated to facilitate the alkylation step of the process. The  
10 bromination is achieved by reacting the 6-hydroxymethyl intermediate (b) with an excess of a brominating reagent which replaces the terminal hydroxy moiety with a bromine atom. Preferred reagents for the brominating step are identified in Piper, et al, *The Journal of Organic*  
15 *Chemistry*, Volume 42:208 (1977). The most preferred reagent is dibromotriphenylphosphine, and subsequent work up and recrystallization from acetic acid and isopropanol yields the hydrogen bromide isopropanol salt of 6-bromomethyl pteridine (c) in high yield.

- 20 This intermediate salt (c) is then reacted with carbonyl compounds under Wittig reaction conditions to form the 9,10-dehydro pteroate ester intermediate (d). The most preferred intermediate (d) is shown as the

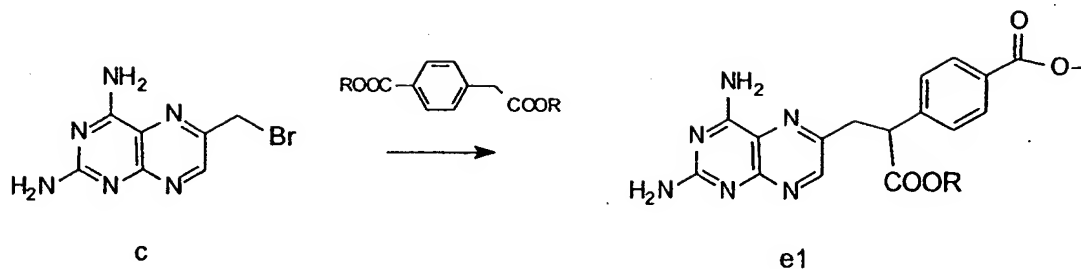
methyl ester of 9,10-dehydro pteronic acid. Preferred reagents used in the reaction are triphenylphosphine and methyl-4-formyl benzoate, in a strong base such as sodium methoxide, to form the intermediate (d).

5       The ester (d) is then reduced to saturate the C9-C10 bond. The preferred process involves reacting the ester intermediate (d) with palladium/carbon palladium on alumina in an organic solvent to produce intermediate methyl pteronate ester (e).

10       The methyl pteronate ester (e) is then converted to the key pteronic acid intermediate (f), 4-amino-4-deoxy-10-deaza pteronic acid. Preferably the hydrolysis is conducted in a strong base, most preferably in aqueous sodium hydroxide solution along with an organic solvent  
15   2-methoxyethanol.

      The pteronic acid intermediate (f) is then activated, and coupled (as the mixed anhydride) to an ester of  $\gamma$ -methylene glutamic acid to form the esterified form of MDAM, and then hydrolyzed to the active compound (g) of  
20   Formula I.

## Scheme IIa



5            In an alternative alkylation of intermediate (c),  
the bromomethyl pteridine salt (c) is pH neutralized,  
then reacted with a diester of homoterephthalic acid (4-  
carboxybenzoic acid) to form the esterified form of the  
10-carboxy intermediate (e1). Intermediate (e1) is then  
10 decarboxylated and hydrolyzed the other ester group with  
a strong nucleophile to form the key pterioic acid  
intermediate (f). Preferred nucleophilic agents include  
sodium cyanide, most preferably dissolved in  
dimethylsulfoxide (DMSO).

15

The following specific examples illustrate the best  
mode for carrying out the inventive process. The  
examples are disclosed for illustrative purposes only,  
and are not to be considered as limiting the invention to  
20 the precise details set forth.

All NMR data are expressed in parts per million (ppm), and the resonances expressed as follows: s, singlet; d, doublet; t, triplet; br.s., broad singlet; sep, septet; c, complex set of signals, the center of which is provided.

#### Example 1

##### 2,4-diamino-6-hydroxymethyl pteridine

10

Tetraaminopyrimidine sulfate (10 mmoles) was taken up in 40 mL of water and barium chloride (10 mmoles) in 10 mL of water was added. The mixture was placed in a boiling water bath for 10 min. After cooling, the barium chloride was removed by filtration and the solid was washed on the filter with about 10 mL of water. The combined washings and filtrate were made up to 50 mL with water. The solution was added to a solution of 150 mL of 4 M sodium acetate containing dihydroxy acetone (30 mmoles) and cysteine hydrochloride monohydrate (10 mmoles) in a 1 L Erlenmeyer flask and was placed on a rotary shaker at room temperature for 24 hours. After this period, the flask was placed in the cold for several

hours, the precipitate was then collected by suction filtration and washed with cold water. The precipitate was resuspended in 100 mL of water and heated to boiling; if necessary drops of 1N sodium hydroxide solution were added to effect the solution. Norit (0.5 g) was added and the hot solution thoroughly mixed, filtered hot through heated funnel. After cooling to room temperature, the pH was adjusted to 6.0 with 1 N HCl and the flask was placed in the cold for several hours. The precipitate was collected by filtration, washed with cold water, ethanol, (50:50) ethanol-ether, and finally with ether, then dried in vacuo. The yield after an additional recrystallization from water is 55%. The compound exhibited following proton NMR signals in DMSO-d<sub>6</sub>; (ppm) 8.8 (s, 2H, aromatic), 7.6 and 6.6 (broad singlets, 4H, Amino), 5.5 (broad singlet, 1H, hydroxy) and 4.65 (s, 2H, benzylic).

#### Example 2

#### 2,4-diamino-6-bromomethyl pteridine

Solid hydroxymethyl pteridine (110 mmoles) was added to a mixture of Ph<sub>3</sub>PBr<sub>2</sub> (363 mmoles) and dimethylacetamide

(360 mL) in a 2L three necked flask. The mixture was stirred at 20-25° C for 3.5 hours. The solution that formed was treated with drop wise during 15 minutes with 7.2 mL of ethanol and stirred for 15 minutes longer before benzene (1.17 L) was added. A dark oil precipitated, and the mixture was stirred for 30 minutes longer and left to stand overnight. The clear supernatant liquid was decanted from the semi solid precipitate, which was dissolved with stirring in hot glacial acetic acid (600 mL, pre heated to 100°C). The solution was filtered while hot, and the beige, crystalline material that separated from the cooled filtrate was collected after 4 hours at 20-25°C. The ether washed solid (solvated by acetic acid) was recrystallized from isopropanol to give yellow orange platelets, which were washed with ether and dried to yield 50% of the theoretical yield. The compound exhibited following proton NMR signals in DMSO-d<sub>6</sub>; (ppm) 9.3 and 9.2 (broad singlet, 4H, amino groups), 9.0 (s, 1H, aromatic), 4.9 (s, 2H, benzylic), 3.8 (septet, 1H, CH of isopropanol), and 1.0 (d, 6H, methyls of isopropanol).

## Example 3

Methyl-9,10-dehydro-4-amino-4-deoxy pterate

5        100 grams of the intermediate from Example 2 above  
was stirred in a solution of 3.0 liters of N,N-  
dimethylacetamide and one molar equivalent of  
triphenylphosphine for 4 hours at 80° C. The solution was  
allowed to cool to room temperature, after which two  
10    molar equivalents of sodium methoxide and one molar  
equivalent of methyl-4-formyl benzoate were added, and  
stirred for 18 more hours. The solution was then diluted  
with 12.0 liters of distilled water and the precipitate  
was filtered under suction and then washed successively  
15    with 200 mL of toluene and diethyl ether. The solid was  
then dried under a vacuum, to yield 62.0 grams of the  
title compound (75% yield).

<sup>1</sup>H NMR: 8.85δ (s,1H); 8.0δ-7.65δ (d,4H); 7.85δ-7.5δ  
(d,2H); 3.8δ (s,3H).

20



## Example 4

Methyl-4-amino-4-deoxy pteroate

5        40 grams of the intermediate from Example 3 above  
was dissolved in 10.0 liters of glacial acetic acid, and  
20.0 grams of 10% palladium on carbon catalyst added and  
hydrogenated at ambient temperature and pressure. The  
reaction was stopped after 24 hours and the palladium  
10    filtered out of the solution. The filtrate was then  
heated to 45° C and purged with air for four hours and  
evaporated the solvent or in alternate method the  
filtrate was diluted with 3.0 liters of 3% hydrogen  
peroxide and stirred four more hours at room temperature.  
15    Evaporation of the solvent at reduced pressure yielded  
32.0 grams of the title compound representing a yield of  
80%.

<sup>1</sup>H NMR: 8.5δ (s,1H); 7.82δ-7.4δ (d,4H); 7.45δ-6.5δ  
(br.s 4H); 3.8δ (s,3H); 3.1δ (s,4H).

## Example 5

4-Amino-4-deoxy pteronic Acid

5        20.0 grams of the intermediate from Example 4,  
above, was dissolved and stirred in 500 mL of 0.5 N  
sodium hydroxide and 500 mL of 2-methoxyethanol at room  
temperature for 24 hours. The solution was concentrated  
to 100 mL, filtered, and the filtrate acidified with  
10    glacial acetic acid to pH 4.5. A copious yellow  
precipitate formed and was refrigerated overnight, then  
filtered, washed with distilled water and dried. The  
crude product was determined to be 90% pure by HPLC, and  
resulted in the recovery of 17.0 grams of the title  
15    compound (90% yield).

$^1\text{H}$  NMR: 8.45 $\delta$  (s, 1H); 7.8 $\delta$ -7.3 $\delta$  (d, 4H); 7.5 $\delta$ -6.7 $\delta$   
(br.s, 4H); 3.1 $\delta$  (s, 4H).

MS (FAB): 310

20

## Example 6

Methyl-4-amino-4-deoxy-10-methoxycarbonyl-pterolate

5        3.0 grams of dimethyl homoterephthalate is slowly added to a stirred suspension of 1.64 grams of 35% potassium hydride in mineral oil and 12 mL of dry N,N-dimethyl formamide which has been cooled to 0° C. After 30 minutes the yellow solution was cooled to -40° C, and 10    1.42 grams of 6-bromomethyl pteridine hydrogen bromide (0.33 molar equivalents) in 5 mL of dry DMF was added over a period of 10 minutes. Alternatively, one molar equivalent of 6-bromomethyl pteridine may be used. The mixture was brought to room temperature and stirred for 15    two more hours. The solvent was then removed by vacuum, and the residue was extracted with chloroform and then dried over anhydrous magnesium sulfate, then concentrated in vacuo to yield 2.0 grams (~60% yield) of the title compound.

20        <sup>1</sup>H NMR: 8.8δ (s,1H); 7.9δ-7.3δ (d,4H); 7.6δ-6.6δ (br.s,4H); 4.62δ (t,1H); 3.5δ-3.55δ (s,6H); 3.3δ-3.5δ (m,2H).

## Example 7

4-amino-4-deoxy-pteronic acid

5           0.55 grams (1.44 mmoles) of the intermediate from  
Example 7 above, and 0.21 grams (4.32 mmoles) of sodium  
cyanide were dissolved in 10 mL of dimethylsulfoxide and  
stirred for 3 hours at 175° C-180° C for 3 hours. The  
dark mixture was cooled, and the solvent removed by  
10 vacuum. The residue was dissolved in 15 mL of distilled  
water, filtered, and the filtrate acidified with glacial  
acetic acid. The precipitate was collected and washed  
with water to obtain 0.41 grams of crude pteronic acid in  
quantitative yield.

15           <sup>1</sup>H NMR: 8.45δ (s,1H); 7.8δ-7.3δ (d,4H); 7.5δ-6.7δ  
(br.s,4H); 3.1δ (s,4H).

MS (FAB): 310

20           The pteronic acid intermediate is coupled with γ-  
methylene glutamic acid (or an ester thereof) to form  
MDAM. The coupling process is carried out as described  
in any of the above referenced patents or publications.

Further synthesis of Formula II compounds may be carried out as disclosed in PCT Publication WO 91/10666, published July 25, 1991.

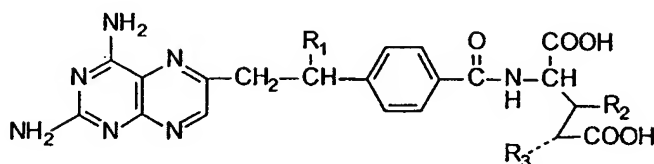
The above description does not limit the invention  
5 to the details given above, but may be modified within  
the scope of the following claims.

What Is Claimed Is:

1. A process for synthesizing a compound of the formula:

5

(II)



wherein R<sub>1</sub> is hydrogen or lower alkyl;

R<sub>2</sub> is hydrogen or hydroxy;

R<sub>3</sub> is hydrogen or methylene; and

10

the dashed line indicates a single bond or a double bond;

said process comprising the steps of:

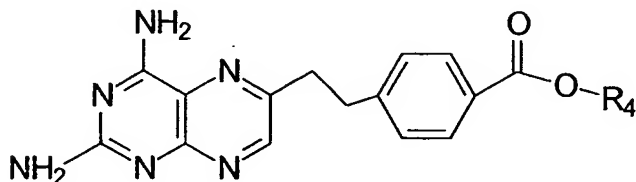
a) providing a starting reagent 2,4,5,6-tetraamino  
15 pyrimidine, or a salt thereof;

b) reacting the starting reagent with 1,3-dihydroxy-2-propanone to form the intermediate compound, 6-hydroxymethyl pteridine;

c) reacting the intermediate compound with a  
20 brominating agent to form 6-bromomethyl pteridine;

d) alkylating the 6-bromomethyl pteridine to form an esterified intermediate of the formula:

(IV)



wherein R<sub>4</sub> is hydrogen or lower alkyl;

e) hydrolyzing the formula IV compound to form the acid homologue thereof;

f) reacting the acid homologue of the formula IV compound with a  $\gamma$ -methylene glutamate ester to form an esterified form of the formula II compound; and

g) hydrolyzing the esterified compound of step f)) to form the formula II compound.

2. The process of Claim 1 wherein step d) includes alkylating the 6-bromomethyl pteridine with a homoterephthallic acid ester, then decarboxylation at the 10 position and hydrolysis of the resulting pteroate ester to form the formula IV compound.

3. The process of Claim 1 wherein step d) includes alkylating the 6-bromomethyl pteridine with a 4-acyl benzoic acid ester, then reducing the resulting pteroate ester under catalytic conditions followed by reoxidation  
5 to the formula IV compound.

4. The process of Claim 1 wherein the starting reagent is present as the sulfate salt thereof.

5. The process of Claim 1 wherein step c) includes  
10 brominating the hydroxymethyl intermediate with an excess of dibromotriphenylphosphine in an organic solvent to form 6-bromomethyl pteridine hydrogen bromide salt.

6. The process of Claim 5 wherein step c) further  
15 includes recrystallizing the hydrogen bromide salt in an alcohol and acid mixture to form the hydrogen bromide isopropanol salt of 6-bromomethyl pteridine.

7. A process for producing  $\gamma$ -methylene-10-  
20 deazaaminopterin comprising the steps of:

a) providing as a starting reagent 2,4,5,6-tetraamino pyrimidine, or a salt thereof;

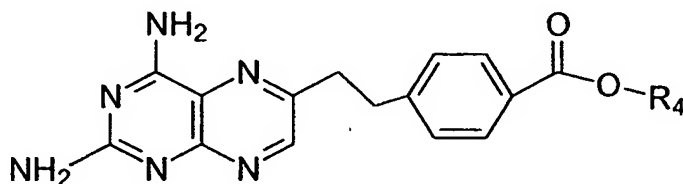


b) reacting the starting reagent with 1,3-dihydroxy-2-propanone to form the intermediate compound, 6-hydroxymethyl pteridine;

c) reacting the intermediate compound with a  
5 brominating agent to form 6-bromomethyl pteridine;

d) alkylating the 6-bromomethyl pteridine to form an esterified intermediate of the formula:

(IV)



10 wherein R<sub>4</sub> is hydrogen or lower alkyl;

e) hydrolyzing the formula IV compound to form the acid analog thereof;

f) reacting the acid homologue of the formula IV compound with a diethyl  $\gamma$ -methylene glutamate to form  
15 an esterified form of  $\gamma$ -methylene-10-deazaaminopterin; and

g) hydrolyzing the esterified compound of step f) to form  $\gamma$ -methylene-10-deazaaminopterin.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/21743

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 475/08

US CL :544/258, 260

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/258, 260

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA file, CA PLUS UNPATFULL

CAS REACT

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,684,653 A (TAYLOR et al.) 1987, column 7, lines 1-11 and 32-48.	1-7
Y	US 5,374,726 A (DEGRAW et al.) 20 December 1994, columns 3-4 Scheme II, lines 13-68.	1-7
Y	US 4,369,319 A (DEGRAW et al.) 18 January 1983, columns 3-4 "STAGE 7", "STAGE 8" to column 6, line 11. line 65.	1-7
Y	US 4,753,939 A (DEGRAW et al.) 28 June 1988, columns 3-4 "STAGE 7" to "STAGE 9", line 65.	1-7
Y	US 5,073,554 A (M. G. NAIR) 17 December 1991, columns 7-8 "SCHEME 2" to column 10, line 11.	1-7

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 MARCH 1998

Date of mailing of the international search report

09 MAR 1998

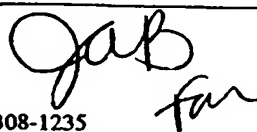
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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,996,207 A (NAIR et al.) 26 February 1991, column 6, lines 30-68, column 11, lines 1-37.	1-7
Y	BAUGH et al. The Synthesis of 6 Hydroxymethylpteridines. J. Org. Chem. 1964, Vol. 23, pages 3610-3612, especially page 3610, column 1 through paragraph bridging column 2.	1-7
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